A Phase 4, Observational Study Evaluating the Efficacy and Safety of the Bruton Tyrosine Kinase Inhibitor (BTKi) Zanubrutinib in Patients with Waldenström Macroglobulinemia (WM)

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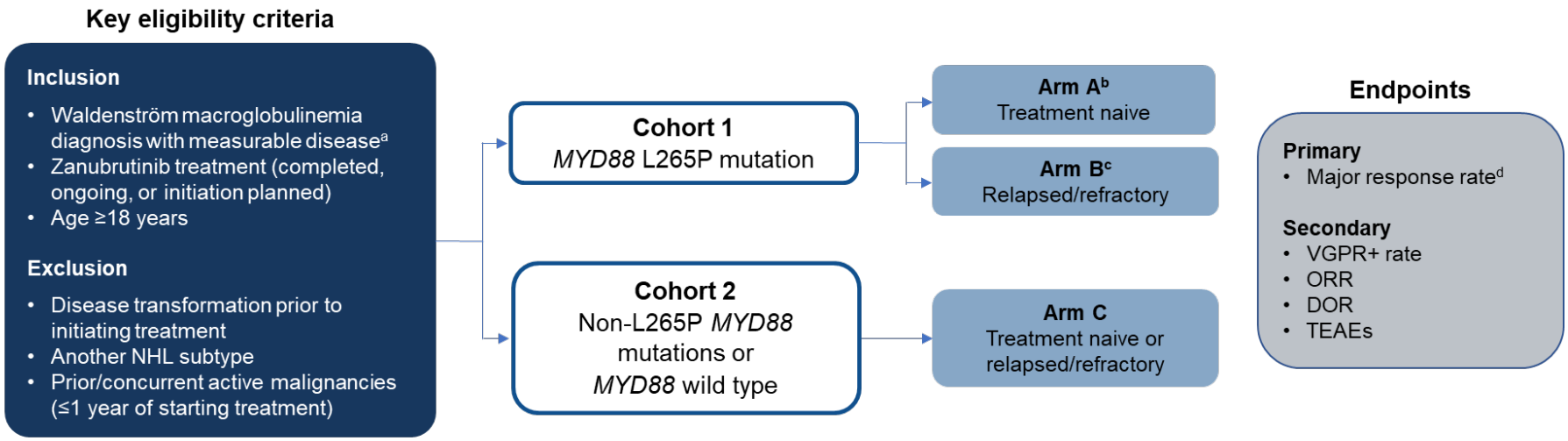
Background and Significance: Zanubrutinib, a next-generation, selective BTKi, is approved for treatment of WM based on data from the phase 3 ASPEN study (NCT03053440), in which zanubrutinib showed a favorable benefit-risk profile vs ibrutinib, a first-generation BTKi, in patients with symptomatic WM (Tam CS, et al. *Blood*. 2020;136:2038-2050). In ASPEN, zanubrutinib showed consistent efficacy across patient subgroups, including prior treatment status (treatment naive or relapsed/refractory) and *MYD88* mutational status (shown to affect prognosis and response to treatment). This registry study will contribute to a more inclusive evidence base for zanubrutinib treatment in populations underrepresented in previous clinical studies, specifically patients who are treatment naive, have non-L265 *MYD88* mutations, or are from racial and ethnic minority groups.

Study Design and Methods: This is a hybrid (retrospective and prospective), multicenter (US only), noninterventional registry study (NCT05640102) in adult patients (aged ≥18 years) with a histologically confirmed diagnosis of WM who are either receiving or planning to initiate zanubrutinib treatment (Figure). Patients with measurable disease (immunoglobulin M level >0.5 g/dL) at zanubrutinib initiation are eligible. Patients with disease transformation prior to zanubrutinib initiation, other non-Hodgkin lymphoma subtypes, or other malignancies (active or in the past ≤1 year) are excluded. Patients will be assigned to 1 of 2 cohorts based on *MYD88* status determined using bone marrow specimens. Cohort 1 will include patients with *MYD88* L265P mutations who are treatment naive (arm A) or have relapsed/refractory disease (arm B). Arm A will enroll mostly patients from racial and ethnic minority groups (Black/African American, Asian, Indigenous/Native American, Native Hawaiian/Other Pacific Islander, and Hispanic/Latino), and arm B will only enroll patients from racial and ethnic minority groups. Cohort 2 will include patients with non-L265P *MYD88* mutations or *MYD88* wild type who are treatment naive or have relapsed/refractory disease in a single arm (arm C). The dose and duration of zanubrutinib treatment is at the discretion of the prescribing physician. Data collection will occur at screening, every 3 cycles during year 1 of zanubrutinib treatment, and every 6 cycles thereafter (28-day cycles). The primary endpoint is the major response rate (MRR) per investigator using Sixth International Workshop on Waldenström Macroglobulinemia response criteria (Owen RG, et al. *Br J Haematol.* 2013;160:171-176). Secondary endpoints are very good partial response or better (VGPR+) rate, overall response rate (ORR), duration of response (DOR), and treatment-emergent adverse events. Efficacy and safety analyses will be conducted descriptively for each study arm. MRR, VGPR+ rate, and ORR will be presented with 95% CIs, and median DOR will be estimated with the Kaplan-Meier method. The study is currently open for enrollment.

Figure. Study Design



DOR, duration of response; IgM, immunoglobulin M; NHL, non-Hodgkin lymphoma; ORR, overall response rate; TEAE, treatment-emergent adverse event; VGPR+, very good partial response or better.
[a] Histologically confirmed diagnosis with measurable disease defined as IgM level >0.5 g/dL at zanubrutinib initiation. [b] Will mostly include patients from the following racial and ethnic minority groups: Black/African American, Asian, Indigenous/Native American, Native Hawaiian/Other Pacific Islander, and Hispanic/Latino. [c] Will only include patients from racial and ethnic minority groups. [d] Assessed per investigator using Sixth International Workshop on Waldenström Macroglobulinemia response criteria (Owen RG, et al. *Br J Haematol*. 2013;160:171-176).